CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761178Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761178
PDUFA Goal Date	June 7, 2021
OSE RCM #	2020-1503
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Deputy Division Director	Doris Auth, PharmD
Review Completion Date	June 7, 2021
Subject	Evaluation of Need for a REMS
Established Name	Aducanumab
Trade Name	Aduhelm
Name of Applicant	Biogen Inc.
Therapeutic Class	Anti-Amyloid Beta Monoclonal Antibody
Formulation(s)	Solution for injection
Dosing Regimen	Treatment initiation: titration based on schedule below

Intravenous infusion (every 4 weeks)	Dosage
Infusion 1 and 2	1 mg/kg
Infusion 3 and 4	3 mg/kg
Infusion 5 and 6	6 mg/kg
Infusion 7 and beyond	10 mg/kg

Maintenance dose:
10 mg/kg administered by intravenous infusion every 4 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Aduhelm (aducanumab) is necessary to ensure the benefits outweigh its risks. Biogen submitted a Biologics Licensing Application (BLA) 761178 for aducanumab, an amyloid beta directed antibody with the proposed indication to delay clinical decline in patients with Alzheimer's disease.

Alzheimer's disease is the most common cause of dementia and a leading cause of morbidity and mortality. Current treatment options are limited and target symptoms only. The efficacy of aducanumab in Alzheimer's disease was evaluated in two pivotal phase 3 trials, Study 301 and Study 302. A phase 1b dose ranging study, Study 103, provided additional data. During the course of the review, it was determined the application would be reviewed under the accelerated approval pathway based on the reduction of amyloid beta plaques seen in Studies 301, 302, and 103; therefore, the indication was revised to "Aduhelm is indicated for the treatment of Alzheimer's disease" .

The main risks associated with aducanumab are amyloid related imaging abnormalities (ARIA), including ARIA-edema (ARIA-E) and ARIA-hemosiderin deposition (ARIA-H). The clinical trials included scheduled MRI monitoring and a dose management protocol. In many cases, ARIA was observed only as a radiographic finding, without associated clinical symptoms. Among patients with ARIA, clinical symptoms were present in 24% of the aducanumab 10 mg/kg treated patients compared to 5% on placebo. Serious adverse events (SAEs) of ARIA occurred in 2% of the aducanumab 10 mg/kg treated patients compared to 0.2% on placebo. Among patients with ARIA, SAEs were reported in 0.4% of the aducanumab 10 mg/kg treated patients compared to none on placebo. The majority of the cases of ARIA occurred within the first 8 months of treatment. Most ARIA events resolved radiographically and, if present, symptoms typically resolved. No deaths were attributed to ARIA. Cases of ARIA have been observed in clinical development programs for other investigational anti-amyloid beta antibodies and published in the literature over the past decade.

The applicant voluntarily submitted a REMS consisting of a communication plan (CP) and a timetable for submission of assessments to address the risk of ARIA-E. The proposed CP included (b) (4)

If approved, aducanumab would be the first anti-amyloid beta antibody approved for Alzheimer's disease and the first agent with the risk of ARIA on the market.

DRM and Division of Neurology 1 (DN1) have determined that a REMS is not needed to ensure the benefits of aducanumab outweigh its risks. The prescribing population will likely consist of memory disorder specialists who are familiar with Alzheimer's disease. Labeling will be used to communicate the risk of ARIA. DN1 has determined that the risk of ARIA does not warrant a boxed warning and can be communicated through Section 5: Warnings and Precautions. Labeling will convey the risk of ARIA and

include recommendations for MRI monitoring, radiographic classification criteria for ARIA severity, the need for assessment of symptoms associated with ARIA throughout treatment, and considerations for continuing aducanumab in the setting of ARIA. A Medication Guide will communicate the risks to patients and caregivers. Post-marketing requirements include a confirmatory study as well as additional pharmacovigilance for the risk of ARIA. If new safety information becomes available, DRM can re-evaluate the need for a REMS.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Aduhelm (aducanumab) is necessary to ensure the benefits outweigh its risks. Biogen (hereafter refer to as the Applicant) submitted a Biologics Licensing Application (BLA) 761178 for aducanumab with the proposed indication to delay clinical decline in patients with Alzheimer's disease.[1] This application is under review in the Division of Neurology 1. The risks associated with aducanumab are amyloid related imaging abnormalities (ARIA), including ARIA-edema (ARIA-E) and ARIA-hemosiderin deposition (ARIA-H). The Applicant submitted a REMS for the risk of ARIA-E. The Applicant's proposed REMS consists of (b) (4)

During the review cycle it was determined the application would be reviewed under the accelerated approval pathway; therefore, the proposed indication was revised to "Aduhelm is indicated for the treatment of Alzheimer's disease". This indication is eligible for the accelerated approval pathway based on the reduction in amyloid beta plaques observed in patients treated with Aduhelm.[a]

2 Background

2.1 PRODUCT INFORMATION

Aduhelm (aducanumab), BLA 761178, a new molecular entity[b], is a human immunoglobulin gamma 1 (IgG1) monoclonal antibody that binds to aggregated soluble and insoluble forms of amyloid beta.[2] The two pathologic hallmarks of Alzheimer's disease include extracellular deposits of amyloid beta and neurofibrillary tangles comprised of hyperphosphorylated tau. Accumulation of amyloid beta in the brain is proposed to be a primary driver of neurodegeneration. Aducanumab reduces amyloid plaques that accumulate in the brains of people with Alzheimer's disease.[3,4]

[a] Under accelerated approval the Applicant must further study aducanumab to verify the benefit. If confirmatory trials do not show benefit, it could lead to removing the drug from the market.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

The proposed dosage for aducanumab is 10 mg/kg administered as an intravenous infusion every 4 weeks after an initial dose titration described in Table 1. Aducanumab is intended as a chronic therapy.[c] Aducanumab will most likely be administered in settings, such as infusion centers and provider clinics/offices. Aducanumab is not approved in any jurisdiction at this time. Aducanumab was granted fast track designation, priority review, and is being reviewed under the accelerated approval pathway. If approved, aducanumab would be the first anti-amyloid beta antibody approved for the treatment of Alzheimer's disease.

Table 1. Dosing Schedule for Treatment Initiation

Intravenous infusion (every 4 weeks)	Dosage (administered over approximately one hour)
Infusion 1 and 2	1 mg/kg
Infusion 3 and 4	3 mg/kg
Infusion 5 and 6	6 mg/kg
Infusion 7 and beyond	10 mg/kg

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761178 relevant to this review:

- **08/19/2016:** Fast track designation granted for treatment of Alzheimer's disease.
- **03/21/2019**: The Applicant terminated the Phase 3 Program (Studies 301 and 302) based on the results of a pre-specified futility analysis.
- **06/2019 to 06/2020:** Type C Meetings held between the Applicant and the Agency to discuss aducanumab pivotal study data analyses and possible path forward for BLA submission.
- **07/07/2020:** The final components of the rolling submission for BLA 761178 received. The submission contained a proposed CP REMS (b) (4)
- **08/06/2020:** The Application was granted Priority review.
- **09/30/2020:** A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Applicant was informed that the REMS determination was ongoing.
- **11/06/2020:** Peripheral and Central Nervous System Drugs Advisory Committee Meeting was convened to discuss BLA 761178 for the treatment of Alzheimer's disease.[2,5] The primary discussion was the data supporting the effectiveness of aducanumab in the setting of early termination of the pivotal, phase 3 trials due to a pre-specified futility analysis as well as the discordant results of the trials when analyzed individually. The REMS Proposal was not discussed. The overall consensus of the panel was that data from Study 302 alone did not

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

support the approval of aducanumab for the treatment of Alzheimer's disease. See Appendix 10.2 for Table 3 for a summary of the panel discussion and vote.

- **01/28/2021:** The Agency issued a Major Amendment Acknowledgement Letter to the Applicant extending the PDUFA goal date 3 months.[6]

- **04/28/2021:** A meeting was held between the Agency and the Applicant via teleconference. The Applicant was informed that the application was being reviewed under accelerated approval pathway on the basis of reduction in amyloid plaques.

- **05/06/2021:** A meeting was held between the Agency and the Applicant via teleconference to discuss the planned communication strategies and educational campaign to communicate the risk of ARIA associated with aducanumab to prescribers and radiologists.

- **05/11/2021:** A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Applicant was informed that the need for a REMS remains under review.

- **06/03/2021:** The Agency informed the Applicant a REMS was not needed to ensure the benefits of aducanumab outweigh its risks.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Alzheimer's disease is a progressive, degenerative neurologic disorder characterized by progressive memory loss, behavioral problems, and inability to perform activities of daily living.[7] Alzheimer's disease is the most common cause of dementia and a leading cause of morbidity and mortality in the aging population. About 5.8 million people in the United States (US) suffer from Alzheimer's disease.[d] Without interventions to prevent or slow the disease, it has been projected that this number could increase to 13.8 million by 2050. It is currently the sixth leading cause of death in the US and the fifth leading cause of death for people ages 65 and older.[2,8,e]

The clinical course of the disease is a continuum of preclinical disease, mild cognitive impairment, and dementia.[7] Early in the disease, changes may be undetectable in affected patients but progress to subtle problems with memory and thinking, and ultimately difficulties with memory, language, and problem-solving, which limit the individual's ability to perform everyday activities. Patients suffering

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

from Alzheimer's disease experience significant morbidity while living with the disease due to progressive memory loss, behavioral problems, and loss of independence due to inability to perform activities of daily living. The burden associated with Alzheimer's disease is significant due to high direct medical costs as well as the unpaid time family may spend caring for those suffering with the disease.[8] Life expectancy may vary depending on several factors, however, the average survival is 4-8 years after a diagnosis.[2,7]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are currently no therapies that target the pathophysiologic processes or slow the clinical decline of Alzheimer's disease. Current treatment goals are aimed at maintaining quality of life and treatment of cognitive symptoms, and management of behavioral and psychological symptoms of dementia. Available FDA approved drugs are cholinesterase inhibitors (e.g. donepezil, rivastigmine, and galantamine) for the treatment of mild, moderate, and severe Alzheimer's disease dementia and the N-methyl-D-aspartate antagonist, memantine for the treatment of moderate to severe Alzheimer's disease dementia. These agents only provide symptomatic benefits and are less beneficial as the disease progresses.[2] The risks associated with these agents currently approved for Alzheimer's disease are communicated in labeling (see Appendix 10.2 for Table 2). There are no therapies available for early stages of the disease for patients with mild cognitive impairment due to Alzheimer's disease. There is a need for disease-modifying therapies that can slow progression, prolong independence, and maintain quality of life.

4 Benefit Assessment

The efficacy of aducanumab in Alzheimer's disease was evaluated in two pivotal phase 3 trials, Study 301 (NCT02477800) and Study 302 (NCT02484547). An additional phase 1b, dose ranging study, Study 103 (NCT01677572) was cited by the clinical team as supportive evidence for the efficacy of aducanumab.[9]

The two pivotal phase 3 studies were identical in design: multicenter, randomized, double-blind, parallel-group, and placebo controlled. The populations studied in the two phase 3 studies were similar and consisted of patients between the ages 50 to 85 years with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia. The planned study design was an 18-month placebo-controlled treatment period followed by an optional open-label long-term extension period for up to 5 years. These trials were stopped early based on a pre-specified interim analysis for futility. The futility analysis occurred when both studies had reached 50% completion. The Applicant "virtually completed" both trials using "modeling and simulation methodologies" after further review showed statistical significance for Study 302.[9]

The primary endpoint for both pivotal studies was the change from baseline in the clinical dementia rating scale – sum of boxes[f] (CDR-SB) at week 78. Secondary clinical endpoints were changes from baseline on other clinical efficacy scales, the mini-mental state examination (MMSE), Alzheimer's Disease Assessment Scale – Cognitive Subscale-13-Item version (ADAS Cog13), and Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (Mild Cognitive Impairment version) ADCS-ADL-MCI. Additionally, both studies analyzed pharmacodynamic endpoints including the change from baseline in amyloid signal as measured by ^{18}F-florbetapir positron emission tomography (PET) scan in a subset of sites and patients at week 26 and week 78. The standard uptake value ratio (SUVR) was calculated for a composite of brain regions consisting of frontal, parietal, lateral temporal, sensorimotor, and anterior and posterior cingulate, and occipital cortices with whole cerebellum as a reference region.

In Study 302, 1638 patients were randomized 1:1:1 to receive aducanumab low dose (3 or 6 mg/kg after titration), high dose (10 mg/kg after titration)[g], or placebo. Randomization was further stratified by apolipoprotein E (ApoE) ε4 carrier status. The primary efficacy endpoint analysis, change from baseline in CDR-SB at Week 78, demonstrated a statistically significant treatment effect in the aducanumab high-dose treatment arm compared to placebo (-0.39 [-22%]; p=0.0120). Additionally, secondary endpoints demonstrated a significantly significant decline in the high-dose treatment arm. The low-dose arm did not reach statistical significance compared to placebo (-0.25 [-15%], p=0.0901). Aducanumab low dose and high dose resulted in statistically significant reductions in amyloid plaque levels in the brain compared to placebo at weeks 26 and 78. The effects were dose and time dependent and a continued decrease was observed in the long-term extension period.

In Study 301, 1647 patients were randomized 1:1:1 to receive aducanumab low-dose, high-dose, or placebo. No statistically significant differences were observed between aducanumab-treated patients and placebo-treated patients for the primary endpoint. Similar to Study 302, a statistically significant reduction in amyloid plaque levels in the brain was observed.

Study 103 (NCT01677572) provided additional data. Study 103 was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging trial in 197 patients with prodromal AD or mild AD dementia. The study included a 52-week treatment period followed by an optional dose-blind long-term extension. The study was designed to evaluate the safety and tolerability of multiple doses of aducanumab. Secondary outcomes included the effect of aducanumab on brain amyloid plaque content, pharmacokinetics of aducanumab, and immunogenicity. Clinical endpoints were exploratory, and the study was not powered detect differences in clinical endpoints compared to placebo. The 10 mg/kg dose arm showed a reduction, compared to placebo, in the change from baseline in the clinical endpoint CDR-

[f] CDR-SB is an integrated scale with assessments for 3 domains of cognition (memory, orientation, judgement/problem solving) and 3 domains of function (community affairs, home/hobbies, personal care). The "sum of boxes" scoring provides a value from 0 to 18. Higher scores indicate greater disease severity.

[g] In the original protocol, high dose aducanumab in ApoE ε4 carriers was 6 mg/kg after titration. However, this was later modified so that ApoE ε4 carriers randomized to high dose would receive 10 mg/kg after titration. High dose for noncarriers was 10 mg/kg throughout the study.

SB at week 54 (-1.26, 95% CI -2.356, -0.163). Additionally, a statistically significant reduction in amyloid plaque levels was observed at week 26 and week 54 compared to placebo.

Review Team Conclusions[h]

The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness to support approval. The reviewer concluded: "Study 302 provides the primary evidence of effectiveness as a robust and exceptionally persuasive study demonstrating a treatment effect on a clinically meaningful endpoint and reinforced by effects on secondary endpoints, biomarkers, and in relevant subgroups." He noted that "Study 301 does not contribute to the evidence of effectiveness" but "the results of Study 301 are sufficiently well understood that they do not preclude independent consideration of the results of Study 302 and 103". Additionally, he concluded Study 103 provided supportive evidence of effectiveness.[9]

The statistical reviewer concluded that the Applicant did not provide substantial evidence of effectiveness stating: "The totality of the data does not seem to provide sufficient evidence to support the efficacy of the high dose. There is much inconsistency. There is only one positive study at best and a second study which directly conflicts the positive study".[10]

Accelerated Approval Pathway

Based upon the secondary pharmacodynamic endpoints in studies 301, 302 and 103 which showed a statistically significant reduction in amyloid beta plaques compared to placebo, the decision was made to review the Application under the Accelerated Approval pathway. Under accelerated approval the Applicant must further study aducanumab to verify the predicted clinical benefit. If the confirmatory trial does not show that the drug provides clinical benefit, it could lead to removing the drug from the market.

5 Risk Assessment & Safe-Use Conditions

The safety database includes 3,078 subjects from Studies 103, 301 and 302 who were exposed to at least one dose of aducanumab. In the pivotal, phase 3 trials (Studies 301 and 302), 1105 patients were treated with aducanumab 10 mg/kg and 1087 were treated with placebo.[11] In the combined placebo-controlled and long-term extension periods of Study 301 and 302, 834 patients received aducanumab 10 mg/kg monthly for at least 6 months, 551 subjects for at least 12 months, and 309 for at least 18 months.[12]

[h] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

The most common adverse reactions were ARIA, headache, and falls.[12] The clinical safety reviewer notes that the safety of aducanumab in patients with moderate or severe dementia is unknown as these patients were excluded from the pivotal studies.[11]

One case of angioedema and urticaria was reported during aducanumab infusion during the placebo-controlled trials. The clinical safety reviewer recommends communicating the risk of hypersensitivity reactions in Section 5, Warnings and Precautions of the label.[11]

ARIA was an adverse event of special interest and discussed in more depth below (see Section 5.2.1).

5.1 SERIOUS ADVERSE EVENTS[i]

5.1.1 Deaths

There were 31 deaths in the aducanumab clinical development program for aducanumab with 25 deaths occurring in aducanumab-treated patients. In the placebo-controlled period of pooled Studies 301 and 302, the incidence of death in aducanumab-treated subjects was not in excess of the incidence in placebo (0.5% (11/2198) versus 0.5% (5/1087), respectively). In Studies 301 and 302, the 11 deaths were attributed to the following: cardiac arrest (N=3), cerebellar infarction (N=2), cerebrovascular accident, completed suicide, dystonia, lacunar infarction, lung neoplasm malignant, myocardial infarction; pleural mesothelioma; pulmonary embolism, renal failure (each reported in 1 subject)[j]. In the placebo group, the 5 deaths were attributed to: congestive heart failure (N=2), death (N=1), myocardial infarction (N=1), and urosepsis (N=1). In the placebo-controlled period of Study 103, 1 death (cerebrovascular accident) occurred in a subject treated with aducanumab and 1 death (cardiac arrest) occurred in a subject on placebo. Eight additional deaths occurred in the long-term extension periods of Study 301 and 302. Five additional deaths occurred in the long-term extension period of Study 103.

The clinical safety reviewer concluded "there was not an excess of deaths in aducanumab-treated groups compared to placebo-treated groups. Most subjects had underlying risk factors for events with fatal outcome. No deaths were attributed to treatment with aducanumab."[11]

[i] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[j] A total of 11 deaths in the aducanumab group, but some included multiple preferred terms for cause of death.

5.2 ADVERSE EVENT OF SPECIAL INTEREST (AESI)

5.2.1 Amyloid Related Imaging Abnormalities (ARIA)

Aducanumab is associated with a spectrum of abnormal imaging findings detected on brain magnetic resonance imaging (MRI) known as amyloid related imaging abnormalities (ARIA).[k] ARIA is comprised of ARIA-edema (ARIA-E) and ARIA-hemosiderin deposition[l] (ARIA-H). ARIA-H consists of cerebral microhemorrhages, superficial siderosis, and cerebral hemorrhages. Severity of ARIA is based on MRI classification criteria interpreted by radiologists. Clinical symptoms associated with ARIA may include headache, dizziness, confusion, nausea, vomiting, gait disturbances, visual disturbances, and seizures.

The clinical trial protocols for aducanumab included a pre-specified, robust monitoring plan for ARIA incorporating recommendations from a 2011 Alzheimer's Association Research Roundtable Workgroup.[13,14] The protocols included brain MRI monitoring at specific intervals[m] throughout treatment to monitor for ARIA. If ARIA was detected, follow-up brain MRIs were recommended for all patients except those with mild ARIA-H. Monitoring continued every 4 weeks until resolution (ARIA-E) or stabilization (ARIA-H).[13] Management of aducanumab infusions in the setting of ARIA in the clinical trials was based ARIA type (E or H), radiographic severity, and clinical evaluation for presence of symptoms (see Appendix 10.5 for Table 4 and Appendix 10.6 for Table 5). Of note, in patients with radiographically mild ARIA and no clinical symptoms, aducanumab therapy continued in all protocol versions. Aducanumab therapy was suspended in patients with radiographically moderate to severe ARIA and criteria for restarting depended on the presence of symptoms and follow-up brain MRIs. Later versions of the ARIA management protocol allowed for restarting aducanumab at the same dose after an ARIA event and revised the criteria for permanent discontinuation.

ARIA (including both ARIA-E and ARIA-H) was observed in 41.1% of patients treated with aducanumab 10 mg/kg compared to 10.2% treated with placebo in Study 301 and 302 (see Appendix 10.4 for Table 3).

ARIA-E was observed in 35% of patients treated with aducanumab 10 mg/kg compared to 2.7% on placebo with 10% of subjects having more than 1 ARIA-E episode. The incidence of ARIA-E was higher in apolipoprotein E ε4 (ApoE ε4) carriers than in ApoE ε4 non-carriers. Most episodes of ARIA-E occurred within the first 8 infusions (first 8 months of treatment). In patients with ARIA-E who were receiving aducanumab 10 mg/kg, the maximum radiographic severity was classified as mild in 30%, moderate in

[k] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[l] Also may be referred to as ARIA-hemorrhage.

[m] The brain MRI monitoring in clinical trials occurred before the 5th, 7th, 9th, 12th, 15th, 18th, and after the 20th infusions.

58%[n], and severe in 13%. Resolution of ARIA-E events[o] occurred in 68% of patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection.

The frequency of ARIA-H is described in Appendix 10.4, Table 3. Of note, isolated ARIA-H was not imbalanced in the patients treated with aducanumab compared to placebo and patients were more likely to experience ARIA-H in concurrence with ARIA-E. There was no imbalance in macrohemorrhages (defined as greater than 1 cm) between aducanumab and placebo.

The clinical reviewer notes that severe ARIA was "relatively infrequent in those treated with 10 mg/kg aducanumab in the placebo-controlled portion of studies 301 and 302".[15]

Many ARIA events were not associated with clinical symptoms and were identified as a result of the scheduled MRI monitoring in the clinical trial. Among patients with ARIA (both ARIA-E and H), clinical symptoms were present in 24% of patients treated with aducanumab 10 mg/kg compared to 5% on placebo.[15] Symptoms reported in the setting of ARIA in patients treated with aducanumab 10 mg/kg included headache, confusion, delirium, altered mental status, disorientation, dizziness, vertigo, visual disturbance, and nausea. When present, most symptoms were classified as mild to moderate. Symptoms were more likely with radiographically severe ARIA events, however, the clinical reviewer notes that the incidence of severe symptoms remains low.[15] Serious adverse events of ARIA in the placebo-controlled period of the pivotal studies occurred in 2% (17/1105) of subjects in the aducanumab 10 mg/kg group compared to 0.2% (2/1087) in the placebo group. Clinical symptoms resolved in 88% of patients over time.

The clinical safety reviewer systematically reviewed 29 serious ARIA events; 23 occurred during the placebo-controlled periods of studies 301 and 302, and 6 occurred during the long-term extension periods. Symptoms were present in 26/29 cases and primarily consisted of headache, acute confusional state, visual disturbances, gait disturbances, and weakness/motor strength impact. The timing of symptoms varied with symptoms occurring prior to radiographic evidence of ARIA in 13 subjects, concurrently in 4 subjects, and after ARIA was detected in 9 subjects. Serious ARIA events typically occurred between the 2nd and the 11th dose, with most events between the 3rd and 8th dose of aducanumab. Resolution of serious ARIA occurred in almost all cases (28/29), however there were instances of unresolved ARIA symptomatology including continuation of visual disturbances in two subjects. The clinical reviewer notes that "cases of symptomatic, serious ARIA were too few to fully

[n] The clinical reviewer's analysis reports the severity was moderate in 57% and the difference was due to a single patient who had a mild episode in the placebo-controlled portion and moderate in the long-term extension period. The clinical reviewer notes this is not a meaningful difference.

[o] The clinical reviewer's analysis included "radiographic recovery from all episodes of ARIA-E occurred in 60% of cases by 12 weeks, 79% of cases by 16 weeks, 90% of cases by 20 weeks, and 98% of cases overall." The difference was clarified in an information request received on May 27, 2021 and was due to a difference in rounding for the cut off of "12 weeks".

characterize the extent, duration, outcomes, or clinical significance". The clinical reviewer concluded that no deaths were determined to be due to ARIA.[15]

The clinical safety reviewer recommends the risk of ARIA be communicated in labeling in Section 5, Warnings and Precautions and does not recommend a boxed warning based on the data available at this time. The clinical safety reviewer recommends labeling convey recommendations to monitor and mitigate the risk of ARIA. (b) (4)
The optimal MRI monitoring schedule has not been determined as it is not known if detecting radiographic ARIA in the absence of clinical symptoms had a significant safety benefit. However, the clinical reviewer notes that different monitoring and dose modification recommendations from the clinical trial setting may result in a different safety profile than what was observed. The clinical reviewer has recommended MRI monitoring prior to the 7th and 12th infusion, with the rationale that this schedule will provide monitoring during titration prior to the first 10 mg/kg dose, and would allow for better capture of first ARIA events, particularly in cases of ApoE4 carriers. This schedule also aligns with two of the timepoints from the clinical trials and will allow the potential for comparison with post-marketing findings. If aducanumab is approved, the clinical reviewer recommends additional pharmacovigilance for the risk of ARIA in order to provide additional data on the safety of aducanumab in a real-world setting.[15]

6 Expected Post-market Use

The anticipated prescribing population for aducanumab will likely be memory disorder specialists which include neurologists, psychiatrists and geriatricians, who should have experience in the care for patients with Alzheimer's disease.[16] Aducanumab will be likely be administered in settings, such as infusion centers and provider clinics/offices. As aducanumab will require brain MRI evaluation prior to treatment initiation and during therapy, radiologists will be involved in care to identify ARIA and classify radiographic severity. Memory disorder clinics likely include a multi-disciplinary team of specialists and may include neuroradiologists with specialized expertise. ARIA has been observed in clinical development programs for similar investigative agents; therefore, it is possible based on the published reports that memory disorder specialists and neuroradiologists may be aware of the risk of ARIA.

7 Risk Management Activities Proposed by the Applicant

The Applicant proposed risk management activities for aducanumab beyond routine pharmacovigilance and labeling including a REMS.

7.1 Review of Applicant's Proposed REMS

(b) (4)

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8 Discussion of Need for a REMS

Alzheimer's disease is a progressive, degenerative neurologic disorder characterized by progressive memory loss, behavioral problems, and inability to perform activities of daily living.[7] Alzheimer's disease is the most common cause of dementia and a leading cause of morbidity and mortality in the aging population. Current treatment options target symptoms only and do not delay the progression of the disorder.

The efficacy of aducanumab in Alzheimer's disease was evaluated in two pivotal phase 3 trials, Study 301 and Study 302. An additional phase 1b, dose ranging study, Study 103 was cited by the clinical efficacy reviewer as supportive evidence for the efficacy of aducanumab. During the course of the review, it was determined the application would be reviewed under the accelerated approval pathway based on reduction of amyloid beta plaques seen in Studies 301, 302, and 103. Under accelerated approval the Applicant must further study aducanumab to verify the predicted clinical benefit. If the confirmatory trial does not show that the drug provides clinical benefit, it could lead to removing the drug from the market.

Aducanumab is associated with a spectrum of abnormal imaging findings detected on brain MRI known as amyloid related imaging abnormalities (ARIA). Cases of ARIA have been observed in clinical development programs for several investigational anti-amyloid antibodies. The first cases were reported in clinical trials with the anti-amyloid beta monoclonal antibody, bapineuzumab in 2009.[17,18] In 2011, the Alzheimer's Association Research Roundtable convened a workgroup of experts who labeled these MRI abnormalities as ARIA and provided recommendations for monitoring for ARIA in future clinical trials.[14] Since then, ARIA has been associated with additional anti-amyloid antibodies.[19] Spontaneous ARIA-E has been detected rarely in patients with Alzheimer's disease without exposure to anti-amyloid antibodies during clinical trials.[14,20] Cerebral microhemorrhage findings on MRI (ARIA-H) in patients without

exposure to anti-amyloid antibodies have been reported and the prevalence of these findings is increased with older age and in patients with Alzheimer's disease than the general population.[14,21,22]

To mitigate the risk of ARIA-E, the Applicant submitted a REMS that was comprised of a communication plan and a timetable for submission of assessments to mitigate the risk of ARIA-E. The proposed communication plan involved (b) (4)

Given the route of administration (IV infusion) and the need for brain MRI monitoring to detect ARIA, it is anticipated that aducanumab will likely be prescribed by memory disorder specialists (neurologists, geriatricians, and/or psychiatrists) who are familiar with Alzheimer's Disease. Based on the interest in this class of drugs and the availability of published literature, this reviewer believes that some prescribers may be aware of the risk of ARIA associated with this class of drugs.

ARIA (including ARIA-E and H) was observed in 41.1% of patients treated with aducanumab 10 mg/kg compared to 10.2% on placebo. Most patients with ARIA were asymptomatic, therefore ARIA was often only a radiologic finding. Among patients with ARIA, clinical symptoms were present in 24% of the aducanumab 10 mg/kg treated patients compared to 5% on placebo. Serious adverse events (SAEs) of ARIA occurred in 2% of the aducanumab 10 mg/kg treated patients compared to 0.2% on placebo. Among patients with ARIA, SAEs were reported in 0.4% of the aducanumab 10 mg/kg treated patients compared to none on placebo. In the majority of cases, ARIA resolved radiographically over time after detection and symptoms resolved. The risk of ARIA is typically highest early in treatment and seems to decrease over time. Of note, the clinical trials included a robust monitoring plan for ARIA including schedule brain MRI monitoring throughout treatment and a protocol for dosing aducanumab in the setting of ARIA.

DRM did discuss the risk of ARIA with DN1 throughout the review of this application and while ARIA is a novel risk, DN1 has determined that the risk of ARIA does not rise to the level of a boxed warning. DRM generally recommends consideration of a REMS if labeling (i.e. a boxed warning) is not sufficient to ensure the benefits outweigh the risks and additional risk mitigation strategies are necessary. DN1 has determined that the risk of ARIA, communicated through Section 5: Warnings and Precautions in labeling is sufficient. Labeling will convey the risk of ARIA and include recommendations for MRI monitoring, radiographic classification criteria for ARIA severity, the need for assessment of symptoms associated with ARIA throughout treatment, and considerations for continuing aducanumab in the setting of ARIA. A Medication Guide will communicate the risk of ARIA to patients and caregivers. (b) (4) However, given the accelerated approval pathway requires confirmatory trials and the clinical reviewer is recommending additional pharmacovigilance for the risk of ARIA, there should be additional data on the safety of aducanumab in a real-world setting. If new safety information becomes available, DRM can re-evaluate the need for a REMS.

The Applicant has proposed [redacted] (b) (4) DRM does not object the to the proposed voluntary activities; however, as these materials are not part of labeling or a REMS, they should be reviewed by the Office of Prescription Drug Promotion.

Alzheimer's disease is a debilitating disorder and a leading cause of morbidity and mortality in the aging population. There is an unmet medical need for treatments for Alzheimer's disease that can slow its progression. In clinical trials, ARIA was primarily a radiographic finding; most patients with ARIA were asymptomatic. The majority of ARIA resolved radiographically and, if present, clinical symptoms typically resolved as well. DN1 determined the risk of ARIA does not require a boxed warning, but will be conveyed in Section 5, Warnings and Precautions. Labeling will also include recommendations for MRI monitoring, radiographic classification criteria for ARIA severity, the need for assessment of symptoms associated with ARIA throughout treatment, and considerations for continuing aducanumab in the setting of ARIA. Taking all these factors into consideration, DRM recommends that, should aducanumab be approved, a REMS is not warranted at this time to ensure its benefits outweigh its risks.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The labeling will convey the risk of ARIA.

Should DN1 have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

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10.2 TABLE 1. SUMMARY OF PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE PANEL DISCUSSION AND VOTING

Panel Question	Vote	Notes
Does Study 302, viewed independently and without regard for Study 301, provide strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's disease?	Yes: 1; No: 8; Uncertain: 1	The panel discussed challenges viewing Study 302 independently as a positive study without acknowledging the negative results of Study 301. The panel acknowledged that Study 302 met its primary endpoint but had concerns about the weight of the evidence and clinical meaningfulness.
Does Study 103 provide supportive evidence of the effectiveness of aducanumab for the treatment of Alzheimer's disease?	Yes: 0; No: 7; Uncertain: 4	The panel noted that Study 103 was a phase 2 trial designed as a safety and tolerability study and was not powered to evaluate effectiveness of clinical endpoints.
Has the Applicant presented strong evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology?	Yes: 5; No: 0; Uncertain:6	The panel noted that there was evidence of aducanumab's pharmacodynamic effects on reducing amyloid plaques. However, 6 panel members voted that they were uncertain if these biomarker changes were correlated to clinical effects.
In light of the understanding provided by the exploratory analyses of Study 301 and Study 302, along with the results of Study 103 and evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology, is it reasonable to consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease?	Yes: 0; No: 10; Uncertain: 1	The panel had concerns about using Study 302 as the primary evidence of effectiveness. The panel determined it was challenging to draw conclusions based on the available data.

Source: Adapted from PCNS Drugs Advisory Committee Meeting- Final Summary Minutes[5]

10.3 TABLE 2. DRUGS APPROVED IN THE US FOR ALZHEIMER'S DISEASE

Name (generic); Approval Year	Indication	Formulation(s)	Safety and Tolerability Issues	Risk Management Approaches
Aricept; Aricept ODT (donepezil hydrochloride); 1996	Treatment of dementia of the Alzheimer's type. Efficacy has been demonstrated in patients with mild, moderate, and severe Alzheimer's Disease	Oral tablets, oral disintegrating tablets	Safety issues related to increased cholinergic activity including the following: may exaggerate the effects of succinylcholine-type muscle relaxation during anesthesia; cardiac effects (bradycardia, heart block, syncopal episodes); peptic ulcer disease and gastrointestinal (GI) bleeding; nausea and vomiting; weight loss; bladder outflow obstruction; seizures; respiratory adverse events (caution in patients with pulmonary conditions)	Labeling – Warning and Precaution
Exelon (rivastigmine tartrate; rivastigmine transdermal system); 2000	Mild, moderate, and severe dementia of the Alzheimer's type and mild-to-moderate dementia associated with Parkinson's disease (PD)	Oral capsules; oral solution; transdermal patch	Significant gastrointestinal adverse reactions (nausea, vomiting, decreased appetite, weight loss, dehydration); allergic dermatitis; risks due to increased cholinergic activity (same as donepezil above); impairment in driving or use of machinery Patch also includes: hospitalization and rarely death reported due to application of multiple patches at the same time; skin application site reactions	Labeling – Warning and Precaution
Razadyne; Razadyne ER (galantamine hydrobromide); 2001	Treatment of mild to moderate dementia of the Alzheimer's type	Oral immediate release and extended release capsules; oral solution	Serious skin reactions (Stevens Johnson syndrome and acute generalized exanthematous pustulosis), risks due to increased cholinergic activity (same as donepezil above); deaths in subjects with mild cognitive impairment in two randomized trials	Labeling – Warning and Precaution

Namenda, Namenda XR (memantine hydrochloride); 2003	treatment of moderate to severe dementia of the Alzheimer's type	Oral tablets; oral extended release capsules	Genitourinary conditions (decreased urinary elimination of memantine with conditions that increase urinary pH)	Labeling – Warning and Precaution
Namzaric (memantine and donepezil hydrochorides); 2014	treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on 10 mg of donepezil hydrochloride once daily	Oral extended release capsules	Labeled safety issues are outlined for donepezil and memantine above	Labeling – Warning and Precautions

Source: Information obtained from labeling from Drugs@FDA

10.4 TABLE 3. ARIA IN THE PLACEBO-CONTROLLED PERIODS OF STUDIES 301 AND 302

Term	**Aducanumab 10 mg/kg N= 1105 N (%)**	**Placebo N=1087 N (%)**
Subjects with ARIA Events	454 (41.1%)	111 (10.2%)
ARIA-E	387 (35.0%)	29 (2.7%)
Isolated ARIA-E	142 (12.9%)	17 (1.7%)
Isolated ARIA-H	67 (6.1%)	82 (7.5%)
Concurrent ARIA-E and ARIA-H	233 (21.1%)	12 (1.1%)
ARIA-H	312 (28.2%)	94 (8.6%)
ARIA-H (microhemorrhage)	212 (19.2%)	71 (6.5%)
ARIA-H macrohemorrhage	6 (0.5%)	4 (0.4%)
ARIA-H (superficial siderosis)	162 (14.7%)	24 (2.2%)
Isolated ARIA-H microhemorrhage	53 (4.8%)	65 (6%)
Isolated ARIA-H macrohemorrage	2 (0.2%)	2 (0.2%)
Isolated ARIA-H superficial siderosis	12 (1.1%)	13 (1.2%)

Source: Modified from the Clinical Safety Review[15]

10.5 TABLE 4. SUMMARY OF ARIA-E MANAGEMENT PROTOCOLS IN STUDIES 301 AND 302

Clinical Symptom Severity		Radiographic Severity	Protocol Version		
			V1 (20 Apr 2012)	V3 (21 Jul 2016)	V4 (24 Mar 2017) through V6 (28 Jun 2018)
Asymptomatic		Mild	Continue dosing at current dose and schedule		
		Moderate or Severe	Suspend dosing and restart at next **LOWER** dose	Suspend dosing and restart at **SAME** dose	
Symptoms Present	Mild or Moderate	Any			
	Severe		Permanently discontinue		
	Serious "Other medically important event"				
	Serious, except "other than medically important event"		Permanently discontinue		Permanently discontinue

Note: During Protocol V1 (20 Apr 2012), ARIA were counted over 12-week periods. From Protocol V2 (26 May 2016) through Protocol V5 (18 Sep 2017), if a second ARIA event (either ARIA-E or ARIA-H) requires dose suspension, restart at next **lower** dose. If a third ARIA event requires dose suspension, permanently discontinue drug. Beginning with Protocol V6 (28 Jun 2018), a third episode of ARIA that requires dose suspension no longer require study treatment discontinuation, and after recurrent ARIA resolves or stabilizes, restart dosing at same dose.
Note: No participants were enrolled under Protocol V2 (26 May 2016).

Source: Clinical Safety Review for ARIA[15]

10.6 TABLE 5. SUMMARY OF ARIA-H MANAGEMENT PROTOCOLS IN STUDIES 301 AND 302

Clinical Symptom Severity		Radiographic Severity	Protocol Version	
			V1 (20 Apr 2012)	V3 (21 Jul 2016) through V6 (28 Jun 2018)
Asymptomatic		Mild	Continue dosing at current dose and schedule	
		Moderate	Suspend dosing and restart at next **LOWER** dose	Suspend dosing and restart at **SAME** dose
Symptoms Present	Mild or Moderate	Mild or Moderate		
	Severe	Mild or Moderate	Permanently discontinue	
	Serious "Other medically important event"			
	Serious, except "other than medically important event"			Permanently discontinue
Asymptomatic or Symptoms present		Severe	Permanently discontinue	

Note: During Protocol V1 (20 Apr 2012), ARIA were counted over 12-week periods. From Protocol V3 (21 Jul 2016) through Protocol V5 (18 Sep 2017), if a second ARIA event (either ARIA-E or ARIA-H) requires dose suspension, restart at next **lower** dose. If a third ARIA event requires dose suspension, permanently discontinue drug. Beginning with Protocol V6 (28 Jun 2018), a third episode of ARIA that requires dose suspension no longer require study treatment discontinuation, and after recurrent ARIA resolves or stabilizes, restart dosing at same dose.
Note: No participants were enrolled under Protocol V2 (26 May 2016).
Note: Radiographic severity for ARIA-H microhemorrhages counted as follows: ≤ 4 = mild; 5 to 9 = moderate; ≥ 10 = severe. Radiographic severity for ARIA-H superficial siderosis counted as follows: 1 = mild; 2 = moderate; > 2 = severe.

Source: Clinical Safety Review for ARIA[15]

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